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Utilization Pattern for Traditional Chinese Medicine among Late Stage Chronic Kidney Disease Patients: a Hospital-Based Cross-sectional Study

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In Taiwan, chronic kidney disease (CKD) is highly prevalent and traditional Chinese medicine (TCM) is one of the most commonly used complementary medicines. To date, little information is available on the utilization patterns for TCM among CKD patients, particularly those with late stage CKD. We conducted a cross-sectional hospital-based study to investigate this issue. In this study, late stage CKD patients were identified by ICD-9-CM codes: 585 and 586, and only CKD stage 3b, 4 and 5 patients were included in the analysis. Clinical information was retrieved from the electronic medical records database from January, 1, 2006 to December, 31, 2011. Among a total of 8,459 patients, 408 TCM users and 8,051 non-TCM users were identified and their data were analyzed. We found that TCM users were almost four times more likely to be older than 55 years than non-TCM users, after controlling for the other covariates (adjusted odds ratio [aOR]: 3.98, 95% confidence interval [CI]: [2.33, 6.81]). They were also less likely to have diabetes (aOR: 0.48), hypertension (aOR: 0.62) or gout (aOR: 0.62). Among all disease conditions, late stage CKD patients with neoplasms had the highest tendency to seek TCM treatment compared to non-neoplasm CKD patients (aOR: 5.39, 95% CI: [4.64, 6.26]). Among all TCM users, internal medicine outpatient services (providing CHMs only) is more frequently used than acupuncture/massage outpatient services (3,476 vs. 320 visits). Jia-Wei-Xiao-Yao-San (JWXYS) was the most commonly prescribed Chinese herbal medicine (CHM) for late CKD patients (36.2% of 4,494 prescriptions), followed by Bu-Yang-Huan-Wu-Tang (BYHWT)

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(33.1%). This is the first study to identify the characteristics of TCM users among late stage CKD patients and further research targeting the safety and efficacy of the most commonly used CHMs is needed.

Key words: Chronic kidney disease, traditional Chinese medicine, Chinese herbal medicine

Introduction

Chronic kidney disease (CKD) is a global health-care issue which places a great burden on many countries due to the disease's co-morbidities and the need for dialysis therapy to treat end stage renal disease (ESRD) [1,2]. ESRD is a crucial medical issue in Taiwan due to its high prevalence and high incidence (2.58 ‰ vs. 0.36 ‰ in 2010) [3], especially about 7% of the total annual budget of the National Health Insurance (NHI) Program is spent on care of ESRD patients [4].

The utilization of complementary and alternative medicines (CAMs) has been growing in Western countries [5-8]. Traditional Chinese medicine (TCM), as one of the most popular categories of CAM, has always played an important role among Asian populations [9-12]. In Taiwan, TCM have gained increasing popularity since the NHI started to reimburse such services in 1996. Based on previous analyses on administrative claims from the National Health Insurance Research Database (NHIRD) (covering over 96.6% of all 22.4 million of residents in Taiwan in 2001) 25.8% to 28.4% of beneficiaries received TCM from 1996 to 2001 [9]. Chinese herbal medicine (CHM) is one of the most popular modalities of TCM (85.9%) compared with other modalities, such as acupuncture, moxibustion and massage [9,13]. Only CHM prescribed by licensed physicians is reimbursed by the NHI program.

Information on TCM utilization among CKD patients is much needed due to concerns about the potential nephrotoxicity of certain CHMs. In Taiwan, several CHMs containing *Aristolochia debilis*, *Aristolochia manshuriensis* or *Aristolochia fangchi* have been banned since 2003 due to a risk of ESRD and urological malignancies. Nevertheless, whether CHM has positive or negative effect upon CKD/ESRD remains inconclusive [2,14,15]. In addition, little is known about the characteristics of TCM users and the CHMs that are commonly used by CKD patients.

The objective of this study is to explore the utilization patterns of TCM among late stage CKD patients using a hospital-based database. We hypothesized that the co-morbidities of CKD patients were different among TCM and non-TCM users since TCM was thought to be useful in treating chronic and stable diseased condition. Also, there should be commonly used CHM prescribed mainly for CKD. The results of this study may help inform physicians regarding the selection of CHM for CKD patients and development of further relevant study areas.

Materials and Methods

Data Source

We used the hospital-based electronic database of Chang Gung Memorial Hospital (CGMH), a large tertiary hospital system in Taiwan. This database collects comprehensive medical information of

inpatients and outpatients of CGMH, including patient demographics (name, unique identification number, gender, and birth date), diagnoses and procedures rendered during ambulatory visits or admissions, prescription drugs, and laboratory data. Up to five diagnoses, using the International Classification of Diseases, Ninth Revision, and Clinical Modification (ICD-9-CM) codes, are recorded at each visit or admission. The prescription drug data contain information on dosage, frequency, duration, and route of administration for both TCM and Western Medicine (WM). The information contained in this database is stored electronically and available for research purposes.

Subject Selection

Figure 1 depicts the patient selection process. First, patients with ICD-9-CM codes 585 (chronic renal failure) and 586 (renal failure, unspecified) in their medical records between January 1, 2002 and December 31, 2011 were identified. To exclude patients with prevalent CKD, those with ICD-9-CM codes of 585 and 586 before December 31, 2005 were then removed. Moreover, early stage CKD subjects, defined as stage 1, 2 and 3a, were excluded. The recognition of CKD stage was done using the estimated glomerulus filtration rate (eGFR) according to the diagnostic criteria as outlined by the National Kidney Foundation, USA [16]. In this study, eGFR was calculated using the modified Modification of Diet in Renal Disease (MDRD) equation [17].

TCM users were defined as subjects who used TCM, including CHM, acupuncture, moxibustion, and massage, at least once from January 1, 2006 to December 31, 2011. The remaining patients were considered WM (non-TCM) users.

Study Variables

To determine the factors related to utilization of TCM, various demographic characteristics, laboratory data, co-morbidities and reasons for ambulatory visits were used as independent factors. The demographic characteristics included patient's age, gender, and CKD stage. Patients were divided into three age groups: <35 year-old, 35-55 year-old, and >55 year-old. Moreover, the CKD stages of patients were categorized into six groups according to KDIGO classification [16]: CKD stage 1-2 as eGFR $\geq$ 60 mL/min/1.73m^2 with urine albumin/creatinine ratio (ACR) $\geq$ 30 g/mg, stage 3a as eGFR of 45-59 mL/min/1.73m^2, stage 3b as eGFR 44-30 mL/min/1.73m^2, stage 4 as eGFR 29-15 mL/min/1.73m^2, and stage 5 as < 15 mL/min/1.73m^2 or a patient treated with dialysis. Only stage 3b, 4 and 5 patients were included for further analysis. ICD-9 codes were used to identify the co-morbidities of patients and reasons for ambulatory visits. Four co-morbidities commonly seen in CKD patients were chosen [18]: diabetes mellitus (DM), hypertension, hyperlipidemia and gout. The ICD-9 codes are listed in Appendix 1. Additionally, the ICD-9-CM codes during each TCM and non-TCM visit, excluding ICD-9-CM codes 585 and 586, were assigned to various disease categories for the analysis of reasons for ambulatory visits.

Ethics Statement

We obtained ethical approval for this study from the Institutional Review Board of the Chang Gung Memorial Foundation (CGMF) (IRB No.: 101-1523B). Since deidentified data were used, a waiver of informed consent was granted by the Institutional Review Board of the CGMF.

Statistical Analysis

Demographics and co-morbidities were compared between the TCM and non-TCM groups. Descriptive statistics were used for the demographic and clinical characteristics, including mean age, age group, gender, co-morbidities, CKD stage and biochemical profiles. Independent t-tests were used to examine the differences in continuous variables and chi-square tests were used for categorical variables. Additionally, multivariate logistic regression was used to explore the strength of the relationships between the independent factors and TCM use. Moreover, to explore the underlying reasons for ambulatory visits, the disease conditions, presented by ICD-9-CM codes, were recoded into disease categories and compared between TCM and non-TCM visits. To control the independent variables, several parameters, such as sex, gender, ages, and co-morbidities, were adjusted in regression model. Furthermore, TCM prescription analysis was performed across the TCM group to identify the CHM prescription patterns among CKD patients. Frequencies, durations and average dosage of the most commonly used CHMs for CKD patients were identified and the possible pharmacological mechanisms of these CHM were

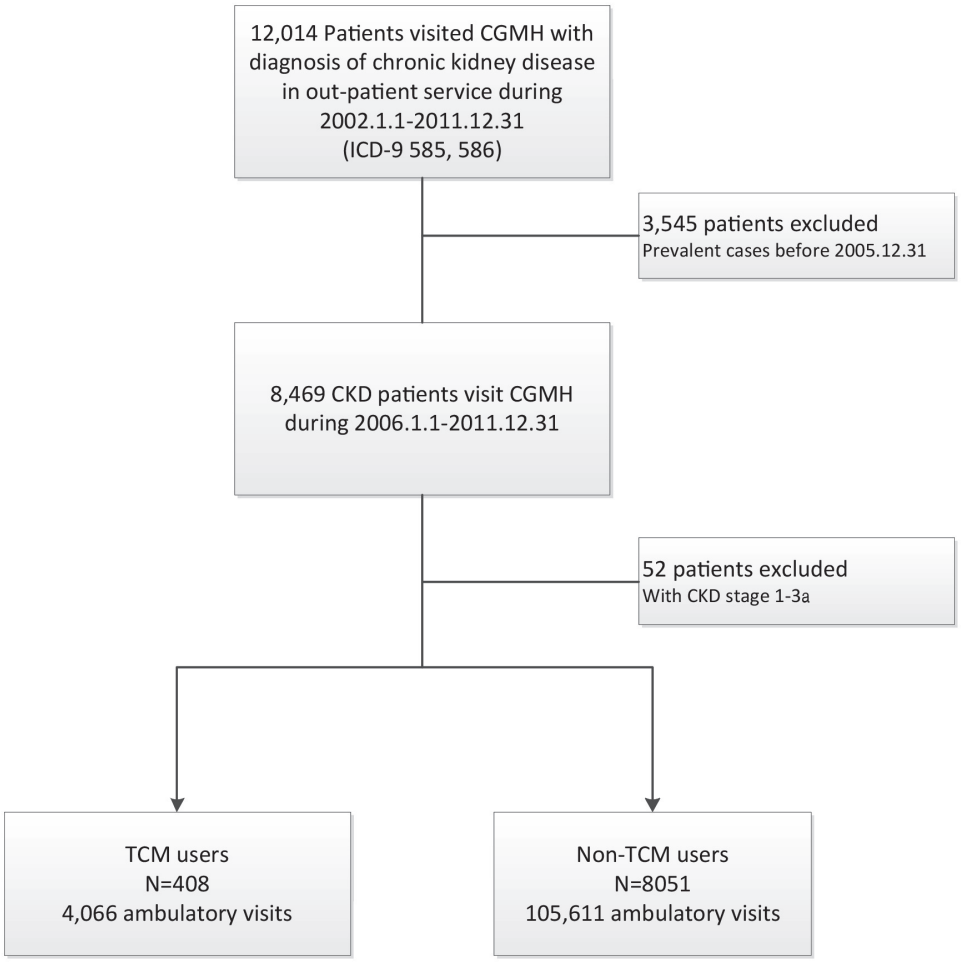

Fig. 1 Flowchart of the subject collection from the CGMH hospital outpatient database from 2006 to 2011 in Taiwan.

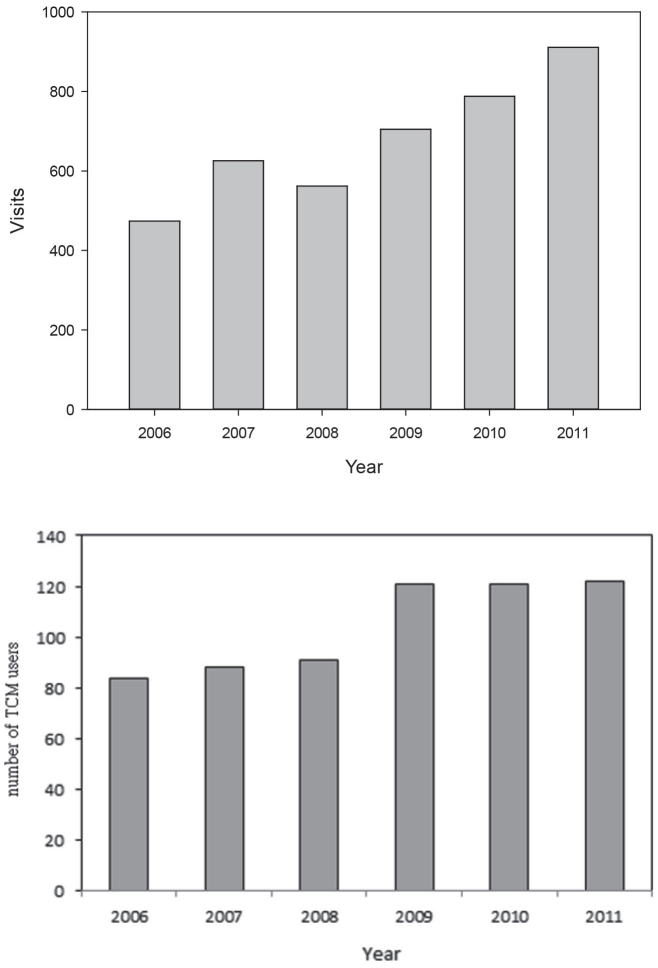

Fig. 2 TCM visits and the number of TCM users of late stage CKD patients at CGMH.

reviewed in Table 6. A *p*-value of less than 0.05 was considered statistically significant. Statistical software SAS version 9.3 was used to analyze the data.

Results

The prevalence of TCM use among late stage CKD patients in CGMH was about 4.8% from January 1, 2006 to December 31, 2011 (Figure 1). The number of visits for TCM and TCM users increased yearly from 2008 to 2011 (Figure 2). Among late stage CKD patients, differences were seen in the clinical and demographic characteristics of TCM and non-TCM users. TCM users were older and less likely to have diabetes, hypertension, or gout (Table 1). In the multivariate regression models, the odds of being a TCM user was almost four-fold if the patient was older than 55 years, after controlling for the other covariates (adjusted odds ratio [aOR]: 3.98, 95% CI: [2.33, 6.81]) (Table 2). In the adjusted models, TCM users were more likely to have hyperlipidemia (aOR: 1.34, 95% CI: [1.04, 1.72]) but 30% to 50% less likely to have diabetes (aOR: 0.48), hypertension (aOR: 0.62) or gout (aOR: 0.62).

A total of 4,066 ambulatory visits were made by 408 TCM users, while 105,611 visits were made by

Table 1. Characteristics of the late stage CKD TCM users from 2006 to 2011 at CGMH.

	TCM users N=408	Non-TCM users N=8051	*p*-value
Age (mean±SD)	52.92±8.88	51.13±10.96	0.0001
< 35 y/o	15(3.8%)	765(9.5%)	0.0001
35-55 y/o	201	3938	
> 55 y/o	192	3306	
Gender			0.016
Male	202(49.5%)	4455(55.3%)	
Female	206(50.5%)	3554(44.7%)	
Co-morbidities			
Diabetes mellitus	93(22.8%)	2873(35.9%)	<0.001
Hypertension	176(43.1%)	4483(56.0%)	<0.001
Gout	41(10.0%)	1176(14.7%)	0.009
Hyperlipidemia	84(20.6%)	1516(18.9%)	0.405
Biochemical profile			
BUN	59.43(29.01)	57.99(29.63)	0.669
Cr	7.84(3.79)	7.27(3.20)	0.170
eGFR	8.98(5.41)	9.32(5.12)	0.108
Na	133.49(5.71)	134.18(5.10)	0.252
K	3.70(0.70)	3.73(0.68)	0.688
Ca	8.27(1.10)	7.98(1.05)	0.017
P	4.24(1.63)	4.39(1.64)	0.461
iPTH	394.69(559.32)	325.01(316.48)	0.413
Hb	8.15(1.46)	8.11(1.54)	0.862

Table 2. Odd ratio for various characteristics compared between TCM users and non-TCM users from 2006 to 2011 at CGMH.

	cOR[†]	[95% CI]	aOR[‡]	[95% CI]	*p*-value
Age					
< 35 y/o	1		1		
35-55 y/o	2.603*	[1.532, 4.424]	3.029	[1.779, 5.157]	<0.0001
> 55 y/o	2.962*	[1.741, 5.039]	3.982	[2.329, 6.809]	<0.0001
Gender					
Female	1		1		
Male	0.782*	[.641, 955]	.880	[.718, 1.079]	0.219
Co-morbidities					
Diabetes mellitus	0.528*	[.417, .668]	.480	[.376, .613]	<0.0001
Hypertension	0.597*	[.488, .729]	.620	[.503, .764]	<0.0001
Gout	0.649*	[.467, .902]	.628	[.448, .880]	.007
Hyperlipidemia	1.110	[0.868, 1.421]	1.336	[1.035, 1.724]	.026
Biochemical profile					
BUN	1.002	[.994, 1.009]			
Cr	1.052	[.979, 1.131]			
GFR	0.986	[0.937, 1.039]			
Na	0.976	[.935, 1.018]			
K	0.935	[.668, 1.305]			
Ca	1.296	[1.049, 1.603]			
P	0.941	[.800, 1.106]			
iPTH	1.001	[0.999, 1.002]			
Hb	1.015	[0.858, 1.201]			

* *p*-value < 0.05

[†] cOR: crude odds ratio

[‡] aOR: adjusted odds ratio

Table 3. Disease encounter for TCM visits among late stage CKD patients.

Disease category	ICD-9	aOR*	[95% CI]	*p*-value
Infectious and parasitic diseases	001-139	.042	[.019, .095]	<0.001
Neoplasms	140-239	5.390	[4.643, 6.257]	<0.001
Endocrine, nutritional and metabolic diseases, and immunity disorders	240-279	.705	[.580,0.858]	<0.001
Diseases of the blood and blood-forming organs	280-289	.175	[.133,.230]	<0.001
Mental disorders	290-319	.693	[.503, .956]	.026
Diseases of the nervous system	320-359	1.890	[1.072, 3.331]	.028
Diseases of the sense organs	360-389	4.766	[2.827, 8.036]	<0.001
Diseases of the circulatory system	390-459	.041	[.036, .048]	<0.001
Diseases of the respiratory system	460-519	1.440	[1.256, 1.651]	<0.001
Diseases of the digestive system	520-579	1.493	[1.326, 1.682]	<0.001
Diseases of the skin and subcutaneous tissue	680-709	1.541	[1.332, 1.783]	<0.001
Diseases of the musculoskeletal system and connective tissue	710-739	.492	[.422, .572]	<0.001

*aOR: adjusted odds ratio

8,051 non-TCM users. 157 TCM users (38.5% in 408 TCM users) were found to receive TCM treatment alone from electronic medical records. Neoplasms were the disease condition most relevant to TCM use compared to non-neoplasm CKD patients (aOR: 5.39, 95% CI: [4.64, 6.26]), followed by diseases of the sense organs (aOR: 4.77, 95% CI: [2.83, 8.04]) and of the nervous system (aOR: 1.89, 95% CI [1.07, 3.33]). In contrast, infectious and circulatory diseases were the disease conditions least associated with TCM visits (Table 3).

Among all TCM users, internal medicine outpatient services (providing CHMs only) were more frequently used than acupuncture/massage outpatient services (3,476 vs. 320 visits). To analysis the reasons for these visits, diseases of neoplasms (7.2% vs. 0.0%, p<0.001) and the respiratory system (59.6% vs. 48.8%, p=0.026) were highly relevant to internal medicine outpatient services, and diseases of the circulatory system (45.9% vs. 40.4%, p=0.003), the skin/ subcutaneous tissue (69.1% vs. 36.1%, p<0.001), and the musculoskeletal system/connective tissue (61.6% vs. 30.0%, p<0.001) were highly relevant to acupuncture/massage outpatient services (Table 4).

Jia-Wei-Xiao-Yao-San (JWXYS) was the most commonly used CHM prescribed for late CKD patients (36.2% of 4,494 prescriptions), while the second most commonly prescribed CHM was Bu-Yang-Huan-Wu-Tang (BYHWT) (33.1%). JWXYS, as one of the most well-known CHMs, has been widely used for various disease conditions, such as anxiety and menstrual disorders. The top ten most commonly used CHM covered not only CKD but also gastrointestinal, respiratory and musculoskeletal disorders. The composition and possible mechanisms of the CHMs are outlined in Table 6.

Table 4. Disease encounter for different TCM visits (internal medicine and acupuncture/message).

Disease category	ICD-9	Internal medicine (N=3476)	Acupunture/ Massage (N=320)	*p*-value
Infectious and parasitic diseases	001-139	6	0	1.000
Neoplasms	140-239	249	0	<0.001*
Endocrine, nutritional and metabolic diseases, and immunity disorders	240-279	885	88	0.133
Diseases of the blood and blood-forming organs	280-289	1004	88	0.793
Mental disorders	290-319	1108	88	0.482
Diseases of the nervous system	320-359	1159	106	0.414
Diseases of the sense organs	360-389	1173	108	0.380
Diseases of the circulatory system	390-459	1404	147	0.003*
Diseases of the respiratory system	460-519	2073	156	0.026*
Diseases of the digestive system	520-579	2472	197	0.111
Diseases of the skin and subcutaneous tissue	680-709	1254	221	<0.001*
Diseases of the musculoskeletal system and connective tissue	710-739	1043	197	<0.001*

* p-value < 0.05

Table 5. Commonly used CHMs at CGMH for late stage CKD (total 4494 visits).

CHM	Dosage (gm/day)	Duration (days)	Counts	Percentage (%)
Jia-Wei-Xiao-Yao-San	5.72	21.26	1628	36.23
Bu-Yang-Huan-Wu-Tang	5.27	21.93	1487	33.09
Gui-Lu-Er-Xian-Jiao	8.24*	22.94	717	15.95
Xiang-Sha-Liu-Jun-Zi-Tang	3.73	20.30	528	11.75
Si-Jun-Zi-Tang	3.10	23.46	414	9.21
Ma-Zi-Ren-Wan	3.75	21.33	400	8.90
Ligustici chuanxiong	2.73	21.86	380	8.46
Xiao-Qing-Long-Tang	4.44	17.88	346	7.70
Ji-Sheng-Shen-Qi-Wan	4.35	19.25	335	7.45
Du-Huo-Ji-Sheng-Tang	3.55	23.10	322	7.17

* pills/day

Table 6. Components and clinical effects of the selected CHMs.

CHM	Ingredients	Previous studies in clinical effects
Jia-wei-xiao-yao-san	*Bupleurum chinense* DC., *Mentha haplocalyx* Briq., *Gardenia jasminoides* J.Ellis, *Paeonia × suffruticosa* Andrews, *Angelica sinensis* (Oliv.) Diels, *Paeonia lactiflora* Pall., *Glycyrrhiza uralensis* Fisch., *Poria cocos* (Schw.) Wolf, *Atractylis lancea* var. *chinensis* (Bunge) Kitam., *Zingiber officinale* Roscoe	Relieved perimenopausal syndrome, such as sleep disturbances, headache and dizziness [28]. Relieved psychological symptoms of postmenopausal syndrome [42]. Increased plasma TNF-alpha levels in depressed menopausal patients [43]. Adjusted gastric motility and improve clinical symptoms in patients with functional dyspepsia [44]. Possessed an antidepressant-like effect at a behavioral and molecular level [45].
Bu-yang-huan-wu-tang	*Astragalus membranaceus* Moench, *Angelica sinensis* (Oliv.) Diels, *Paeonia lactiflora* Pall., *Pheretima aspergillum* E. Perrier, *Ligusticum chuanxiong* S.H.Qiu, Y.Q.Zeng, K.Y.Pan, Y.C.Tang & J.M.Xu, *Prunus persica* (L.) Stokes,, *Carthamus tinctorius* L.	Reduced nitric oxide production and up-regulated Bcl-2 expression of cultured rat cortical neurons under hypoxia [31]. Protected neuron in rat suffering cerebral ischemia-reperfusion damage [32]. Decreased the neuronal nitric oxide synthase activity in rats after permanent focal cerebral ischemia [33]. Protective effect on myocardial ischemia in rats receiving peritoneal injection of isoproterenol [34]. Suppressed the inflammatory cytokines and reactive oxygen species in the kidney of rats after induction of brain death [35].
Xiao-qing-long-tang	*Ephedra sinica* Stapf, *Cinnam-omum cassia* (Nees & T.Nees) J.Presl, *Paeonia lactiflora* Pall., *Glycyrrhiza uralensis* Fisch., *Zingiber officinale* Roscoe, *Asarum sieboldii* Miq., *Pinellia ternata* (Thunb.) Makino, *Schisandra chinensis* (Turcz.) Baill.	Anti-airway inflammatory, anti-airway remodeling, and specific immunoregulatory effects in a chronic asthmatic mice model [46-48]. Prevented bleomycin-induced pulmonary fibrosis in rats [49].
Du-huo-ji-sheng-tang	*Angelica pubescens* Maxim., *Taxillus chinensis* (DC.) Danser, *Eucommia ulmoides* Oliv., *Achyranthes bidentata* Blume, *Asarum sieboldii* Miq., *Gentiana macrophylla* Pall., *Poria cocos* (Schw.) Wolf, *Cinnamomum cassia* (Nees & T.Nees) J.Presl, *Saposhnikovia divaricata* (Turcz.) Schischk., *Ligusticum*	Inhibited VEGF and HIF-1α expression on osteoarthritis rabbits [50].

Table 6. Continued.

	chuanxiong S.H.Qiu, Y.Q.Zeng, K.Y.Pan, Y.C.Tang & J.M.Xu, *Panax ginseng* C.A.Mey., *Glycyrrhiza uralensis* Fisch., *Angelica sinensis* (Oliv.) Diels, *Paeonia lactiflora* Pall., *Rehmannia glutinosa* (Gaertn.) DC.	
Single herb	**Bioactive components**	**Previous studies in clinical effects**
Astragalus membranaceus Moench	Saponins (astragalosides) Flavonoid Polysaccharides	Renal protective effect in diabetic nephropathy [37,39]. Inhibition of oxidative stress and endothelial nitric oxide synthase[38]. Antifibrotic effect [36].
Ligusticum chuanxiong S.H.Qiu, Y.Q.Zeng, K.Y.Pan, Y.C.Tang & J.M.Xu	ferulic acid hydroxyphthalide alkylphthalide diligustilide	Neuroprotection, vasorelaxant, anti-anginal, anti-platelet, anti-oxidative stress and anti-cancer effects [51,52].

Appendix 1. ICD-9-CM codes for co-morbidities.

Co-morbidities	**ICD-9-CM codes**
Diabetes mellitus	250.00, 250.0, 250.02, 250.03, 250.1, 250.10, 250.11, 250.12, 250.13, 250.2, 250.20, 250.21, 250.22, 250.23, 250.3, 250.30, 250.31, 250.32, 250.33, 250.4, 250.40, 250.41, 250.42, 250.43, 250.5, 250.50, 250.51, 250.52, 250.53, 250.6, 250.60, 250.61, 250.62, 250.63, 250.7, 250.70, 250.71, 250.72, 250.73, 250.8, 250.80, 250.81, 250.82, 250.83, 250.9, 250.90, 250.91, 250.92, 250.93
Hypertension	401.0, 401.1, 401.9
Gout	274.0, 274.10, 274.11
Hyperlipidemia	272.0, 272.1, 272.2, 272.3, 272.4

Discussion

In our study, most patients included in this study with ICD-9 codes 585 and 586 were in the late stage of CKD. The prevalence of TCM use among these patients was 4.8% and the number of visits had been increasing from 2006 to 2011. Generally, TCM users were older than non-TCM users among the late stage CKD patients. These findings are consistent with a previous epidemiological study which showed that 50

to 59 year-olds were the most common TCM users, while the lowest usage was observed among 20 to 29 year-olds in Taiwan [19]. Age-related differences in TCM use have been shown in other studies examining healthcare service seeking behavior [19,20].

CKD is a disease condition with various etiologies. Our report showed that DM, hypertension, and gout were less associated with TCM use in this study (Table 3). Polypharmacy may be a possible reason since patients with more co-morbidities might be unwilling to take CHM in addition to multiple WM treatments. The duration of polypharmacy has also been shown to be associated with exacerbation of acute renal failure [21]. In addition, these findings may be consistent with previous studies on TCM that showed TCM users tended to have more regular health checkups and show more health-seeking behaviors [19,22]. Besides, the serum calcium level seems to be higher in TCM users than in non-TCM users (Table 1, 2). Although there are no evidences showing TCM has effect on calcium homeostasis in late stage CKD patients, there may be some characteristics which are attributed to better calcium homeostasis in TCM users, such as more residual function of kidney to process vitamin D to calcitriol, more outdoor exercise or better calcium supplement compliance…etc. However, further research is needed to elucidate the effect of TCM upon calcium homeostasis in late stage CKD patients.

Also, TCM users tended to have other coexisting health problems, such as neoplasm, diseases of the nerve and sense organs, diseases of the digestive system, diseases of the respiratory system, and diseases of the skin and subcutaneous tissue (Table 3). Neoplasm was the most common disease co-existing with late stage CKD among TCM users. In Taiwan, the high prevalence of TCM use among cancer patients may explain the association between TCM and the diagnosis of cancer among CKD patients [23-25]. TCM has been perceived to have fewer side effects than WM, hence its popularity in Taiwan [26]. However, the safety issue of TCM still needs to be illustrated. Some herbal ingredients have been reported to be potential carcinogens and associated with urological malignancies, especially aristolochic acid [27]. In our study, the prevalence of urological malignancies in TCM users was less than in non-TCM users (42.6% vs. 56.7%). Additionally, from the prescription analysis, none of the commonly used CHM contained lethal dose of aristolochic acid or other possible carcinogenic herbs. Therefore, the risk of CHM inducing malignancies may be minimal. Given our cross-sectional study design, we were unable to ascertain the causality between TCM usage and neoplasm occurrences. Further prospective cohort studies with long-term follow-up may be needed to investigate the causal relationship between TCM use and malignancies.

Moreover, there is a high risk of gastrointestinal symptoms in hemodialysis patients, including non-peptic ulcer, and non-variceal gastrointestinal bleeding [28]. TCM as a treatment for digestive disease has been practiced and evaluated [29,30]. These studies imply that TCM may have some effects on improving gastrointestinal symptoms or disorders of bowel movement, which are also common in late stage CKD patients. However, further studies about the efficacy and safety of TCM on digestive disease in CKD patients are also needed.

Among all TCM visits, the majority was provided

by the internal medicine outpatient services, which was consistent with previous analyses from NHIRD [9] and was probably attributed to the fact that private TCM hospitals provided more internal medicine than private TCM clinics in Taiwan [13]. As for all CHM prescriptions, JWXYS and BYHWT were the two most frequently used CHMs and together made up more than two thirds of all prescriptions (Table 5). JWXYS has been widely studied and exhibited clinical effects related to mood stabilization and gastrointestinal motility adjustment [31] (Table 6). It had been reported that there was a high prevalence of depression (about 14% to 30%) among patients with stage 5 CKD who had a low utilization rate of antidepressants [32,33]. Depression may worsen the quality of life of these patients substantially and may also be associated with more frequent hospitalization and a higher mortality rate [32]. In addition, BYHWT was another commonly used CHM among late stage CKD. It has shown to have neural protection and anti-inflammatory properties [34-38] (Table 6). Although there is no direct evidence supporting the efficacy of BYHWT with respect to CKD, the high prevalence of use may be because of one of its major ingredients, *Astragalus membranaceus* Moench (*AMM*). In animal models, *AMM* has been found to have a renal protective effect in relation to diabetic nephropathy, such as the inhibition of oxidative stress and endothelial nitric oxide synthase, as well as an anti-fibrotic effect [39-41]. Furthermore, the clinical effects of AMM have been reviewed in previous studies, including reducing proteinuria, BUN, and creatinine [42]. Further studies are needed due to the high prevalence of BYHWT use among the CHM prescriptions of late stage CKD patients in order to explore the possible pharmacological mechanisms of this CHM.

The other decoctions or single herbs prescribed to the patients in this study are listed in Table 5. Xiang-Sha-Liu-Jun-Zi-Tang, Si-Jun-Zi-Tang and Ma-Zi-Ren-Wan are often prescribed for digestive disorders by TCM physicians. In the ancient TCM literature, these decoctions were said to improve bowel movement and treat syndromes associated with spleen-Qi deficiency, such as poor appetite, tiredness, and distension of the abdomen after eating.

It is the merit of TCM, which takes into account not only the dysfunction of a single organ, but also the individualized body constitution. The basis of TCM concept is to categorize human body condition into heat or cold, repletion or depletion, and return it back to balance by administering corresponding prescriptions to warm or cooling, attacking or supplementing [43]. As a vital feature of medical development in Asian cultures, TCM offers a systematic approach to the treatment of diseases under the specific TCM diagnosis. Based on the TCM diagnosis, individually specific constellation of symptoms is gathered into manifestation patterns (zheng). Different “zheng” is matched with specific categories of herbs or formulas. This concept reflects a distinctive understanding of pathophysiology, constituting an integral aspect of TCM. In other words, it is the integral concept of “zheng” that TCM physicians focus on, instead of the “disease” based on the diagnostic paradigm of WM. Furthermore, CKD is caused by various etiologies and correlated with many co-morbid conditions. It is believed that TCM may cause multi-systematically regulatory effects to heal the body (Table 6). However, it is also the great demerit

of TCM that most of the efficacy and pharmacological mechanism of CHM are still uncertain. These drawbacks are largely overcome by incorporating the idea of "zheng" into clinical trials of CHM. For stage 3 CKD patients with WM treatment, the efficacy of CHM could be maximized while CHM was given simultaneously under the concept of "zheng" [14]. Besides, the quality assurance of herbs is also a crucial issue when using CHM. The misusage of certain toxic species of herbs, such as *Aristolochia* species, had led to several side effects. Provided that the quality of the herbs is assured, potential benefits of CHM as complementary treatment in CKD patients should be explored.

There are several limitations to our study. Firstly, our study did not include health services utilization provided by other hospitals or clinics. Electronic medical records are not exchanged regularly between medical facilities in Taiwan in consideration of patients' privilege and privacy. However, by using a hospital-based database, detailed laboratory data could be gathered without any omissions, providing reasonable validity of laboratory findings. In Taiwan, NHI program fully reimburses for modern powder form of decoctions. However, the self-paid CHMs, such as raw Chinese herbs, and some pill/capsule forms of CHM, are not recorded in NHIRD. Instead of using NHIRD, we can not only collect all prescriptions but also ensure the quality of CHMs by using hospital-based database. Besides, the detection of co-morbidities is more extensive in hospital-based database. The diagnoses of each visit are recorded in the hospital-based database without limitation, but in the NHIRD, only three diagnoses per visit can be saved in the database. Secondly, we restrictively used ICD-9 codes 585 and 586 as the means of enrolling subjects to ensure that most enrollees were late stage CKD patients, which may have underestimated the prevalence of TCM usage in this population. However, by using restrictive diagnosis codes and laboratory data, we were able to identify the study population more precisely. Thirdly, given a cross-sectional study design, we could not track patients' health outcomes over time, such as the frequency of hemodialysis, mortality, and changes in clinical symptoms. The actual percentage of TCM and WM treatments used simultaneously is not accessible in this study due to the uncertainty of patients' drug compliance. A prospective cohort with face-to-face interview and use of detailed questionnaires may be required to gather such information. However, to our knowledge, our study is the first hospital-based cross-sectional analysis of the demographic characteristics of TCM use among late stage CKD patients. Based on these results, further prospective cohort studies that evaluate the efficacy and safety of TCMs prescribed for the late stage CKD population are needed.

Conclusion

For late stage CKD patients, the prevalence of TCM users was around 5% in this hospital-based, cross-sectional study. The TCM users were older and had fewer co-morbidities. Among all diseases, neoplasm was most frequently seen among TCM users. Additionally, JWXYS and BYHWT were the most frequently used CHMs among all prescriptions in our hospital. Researches on both of the nephrotoxicity and potential nephroprotection of CHM are crucial in the

CKD population. Our findings provide some directions for further cohort studies to elucidate the efficacy and safety of these commonly used CHMs among late stage CKD patients.

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Contributions from Authors

The work presented here was carried out in collaboration between all of the authors. TY performed the data collection and manuscript writing. HC analyzed the data and carried out the interpretation. SY, YL, JF, CH and JC designed the methods and helped to revise the manuscript. All authors have contributed to, seen and approved the manuscript.

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晚期慢性腎臟病患者的中醫使用狀況—醫院資料庫橫斷性研究

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慢性腎臟病在台灣具有高盛行率並且中藥也是台灣最普遍使用的替代療法，然而，對於晚期慢性腎臟病患者使用中藥的狀況至今仍缺乏相關調查及研究，因此，我們以 2006 年 1 月至 2011 年 12 月之間長庚紀念醫院院內電子病歷資料庫做了橫斷性研究來分析此一議題。此研究中，我們根據國際疾病碼 (ICD-9-CM codes) 585 及 586 進行搜尋，配合實驗數據分析，找出被診斷為第 3b、4 以及 5 期的晚期慢性腎臟病患者納入此研究。在所有納入研究的 8,459 位患者中，中醫組 (有接受過院內中醫治療) 有 408 位，非中醫組 (未接受過院內中醫治療) 有 8,051 位。研究發現，在控制相關變異之下，發現大於 55 歲以上的族群比較有尋求中醫治療的傾向 (adjusted odds ratio [aOR]: 3.98, 95% confidence interval [CI]: [2.33, 6.81])，此外，我們也發現中醫組較少併見糖尿病 (aOR: 0.48)、高血壓 (aOR: 0.62) 或是痛風 (aOR: 0.62)。在所有併見疾病中，有腫瘤的晚期慢性腎臟病患者有較高尋求中醫治療的傾向 (aOR: 5.39, 95% CI: [4.64, 6.26])。進一步分析中醫組，發現尋求中藥治療的人次較針灸 / 骨傷治療的人次來得多 (3,476 vs. 320 人次)。在所有中藥處方中，加味逍遙散是這些晚期慢性腎臟病患者中最常使用的方劑 (36.2%)，其次為補陽還五湯 (33.1%)。這項研究首次分析晚期慢性腎臟病患者使用中醫的狀況，並可提供將來進一步研究分析相關中藥對這些患者的療效和安全性。

關鍵字：慢性腎臟病、中醫、中藥

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